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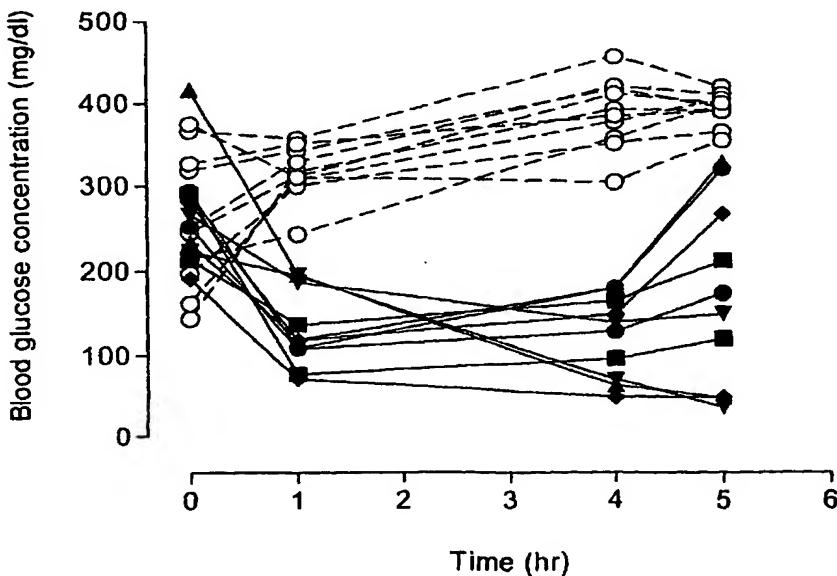
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[Continued on next page]

(54) Title: EMPLOYMENT OF ROTAVIRUS PROTEINS, DERIVED PROTEINS AND PEPTIDES FOR THE MODULATION OF TISSUE PERMEABILITY



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(57) Abstract: The present invention refers to the use of rotavirus proteins VP4, VP8 and their derived fusion proteins and peptides, for enhancing the delivery of pharmaceutical agents through the paracellular pathway. These rotavirus proteins and derived peptides may additionally be employed to reduce unwanted cellular adhesion that can occur between cancerous cells, or between normal cells as a result of surgery, injury, chemotherapy, disease, inflammation or other pathological conditions.



- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- *upon request of the applicant, before the expiration of the time limit referred to in Article 21(2)(a)*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(88) Date of publication of the international search report:  
26 February 2004

## INTERNATIONAL SEARCH REPORT

PCT/IB 03/00280

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07K14/14 A61K39/15 A61K38/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, SEQUENCE SEARCH, EPO-Internal, MEDLINE, WPI Data, PAJ, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 06971 A (UNIV LELAND STANFORD JUNIOR) 10 August 1989 (1989-08-10)  the whole document ----	1-7, 18-21, 23-25, 27,29-42
A	DATABASE EBI Database accession no. P12473 XP002260536  100% identical to Seq-ID-N° 1, 3 in a 776aa overlap; 100% identical to Seq-ID-N° 2 in a 231 aa overlap abstract ---- -/-	1-7, 18-21, 23-25, 27,29-42

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

26 November 2003

Date of mailing of the international search report

02/12/2003

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## INTERNATIONAL SEARCH REPORT

PCT/IB 03/00280

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DORMITZER PHILIP R ET AL: "Proteolysis of monomeric recombinant rotavirus VP4 yields an oligomeric VP5* core" JOURNAL OF VIROLOGY, vol. 75, no. 16, August 2001 (2001-08), pages 7339-7350, XP002260531 ISSN: 0022-538X the whole document & DATABASE EBI Database accession no. Q91HI9  abstract ---	1-7, 18-21, 23-25, 27,29-42
A	TAFAZOLI FARIDEH ET AL: "NSP4 enterotoxin of rotavirus induces paracellular leakage in polarized epithelial cells" JOURNAL OF VIROLOGY, vol. 75, no. 3, February 2001 (2001-02), pages 1540-1546, XP002260532 ISSN: 0022-538X page 1541, column 2 -page 1542, column 1 abstract ---	1-7, 18-21, 23-25, 27,29-37
A	DICKMAN KATHLEEN G ET AL: "Rotavirus alters paracellular permeability and energy metabolism in Caco-2 cells" AMERICAN JOURNAL OF PHYSIOLOGY, vol. 279, no. 4 Part 1, October 2000 (2000-10), pages G757-G766, XP002260533 ISSN: 0002-9513 the whole document ---	1-7, 18-21, 23-25, 27,29-37
A	TIHOVA MARIANA ET AL: "Localization of membrane permeabilization and receptor binding sites on the VP4 hemagglutinin of rotavirus: Implications for cell entry" JOURNAL OF MOLECULAR BIOLOGY, vol. 314, no. 5, 14 December 2001 (2001-12-14), pages 985-992, XP002260534 ISSN: 0022-2836 the whole document ---	1-7, 18-21, 23-25, 27,29-42
T	ZARATE SELENE ET AL: "Interaction of rotaviruses with Hsc70 during cell entry is mediated by VP5." JOURNAL OF VIROLOGY, vol. 77, no. 13, July 2003 (2003-07), pages 7254-7260, XP009020526 ISSN: 0022-538X (ISSN print) -----	1-7, 18-21, 23-25, 27,29-42

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7, 18-21, 23-25, 27, 29-37

Use of Rotavirus protein VP4 and its variants, use of antibodies against VP4, pharmaceutical compositions comprising VP4 or its variants; Methods of Treatment comprising the use of VP4 or its variants and methods for determining regions pf VP4, VP8 that enhance or modulate the opening of the paracellular pathway.

2. Claim : 38

An isolated polypeptide with Seq-ID-N°3

3. Claim : 39

An isolated polypeptide with Seq-ID-N°4

4. Claim : 40

An isolated polypeptide with Seq-ID-N°5

5. Claim : 41

An isolated polypeptide with Seq-ID-N°6

6. Claim : 42

An isolated polypeptide with Seq-ID-N°7

**INTERNATIONAL SEARCH REPORT****PCT/IB 03/00280****Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT****PCT/IB 03/00280**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8906971	A 10-08-1989	WO 8906971 A1	10-08-1989